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Application No.	Filing Date	Examiner	Customer No.	Group Art Unit
09/410,336	**10/01/1999**	**Rawlings, Stephen**	**38732**	**1642**

Invention: **Methods for Identification, Diagnosis and Treatment of Breast Cancer**

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APPEAL BRIEF

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Docket No. **12.006011**

In re Application Of: **Love et al**

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
09/410,336	**10-01-1999**	**Stephen Rawlings**	**000038732**	**1642**	**6727**

Invention: **Methods for Identification, Diagnosis and Treatment of Breast Cancer**

COMMISSIONER FOR PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed on **March 1, 2005**

The fee for filing this Appeal Brief is: **$500.00**

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Attorney's Docket No. 12.006011 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Love et al.		
Appl. No.:	09/410,336	Group Art Unit:	1642
Filed:	October 1, 1999	Examiner:	Stephen Rawlings
For:	MEHODS FOR IDENTIFICATION, DIAGNOSIS, AND TREATMENT OF BREAST CANCER		

April 15, 2005

Commissioner for Patents
Washington, DC 20231

APPEAL BRIEF

Sir:

This Appeal Brief is filed pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed March 1, 2005.

Real Party in Interest.

The real party in interest in this appeal is Cytyc Corporation, Inc., the assignee of the above-referenced patent application.

Related Appeals and Interferences.

There are no related appeals and/or interferences involving this application or its subject matter.

Status of Claims.

Claims 33-39 are the subject of this appeal. The claims appear in Appendix A. No other claims are pending. Claims 1-32 and 40-48 have been cancelled.

Status of Amendments.

In the Advisory Action dated February 2, 2005, the Examiner indicated that the Amendment After Final Rejection filed December 10, 2005 was entered. Thus, all of Applicant's amendments have been entered.

Summary of the Invention.

The pending claims of the present invention are directed to a method of identifying the location of breast cancer cells within a breast duct or breast ductal network by providing a compound comprising a targeting agent coupled to an identifying agent; delivering the compound into at least one breast duct and allowing the delivered compound to specifically bind to at least one breast cancer cell within at least one duct or ductal network; washing the breast duct or ductal network with a solution to remove non-specifically bound compound; and detecting the presence of the identifying agent within the breast duct or ductal network such that the presence of the identifying agent identifies the location of breast cancer cells within the a breast duct or breast ductal network.

Issues.

Issue 1--Whether claims 33 and 36-39 are patentable under 35 U.S.C. § 103(a) as being unpatentable over Yoshimoto et al. (*Breast Cancer Res. Treat.* 42: 87-90, 1997) in view of U.S. Patent No. 5,681,543 A to Schmitt-Willich, et al., and Canto et al. (*Gastrointestinal Endoscopy* 44: 1-7, 1996).

Issue 2-- Whether claims 34 and 35 are patentable under 35 U.S.C. § 103(a) as being unpatentable over Yoshimoto et al. (*Breast Cancer Res. Treat.* 42: 87-90, 1997) in view of U.S. Patent No. 5,681,543 A to Schmitt-Willich, et al., U.S. Patent No. 4,628,027 A to Gay, Canto et al. (*Gastrointestinal Endoscopy* 44: 1-7, 1996), and U.S. Patent No. 6,168,779B1 to Barsky, et al.

Grouping of Claims.

The claims do not stand or fall together. Claims 33 and 36-39 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Yoshimoto *et al.* in view of USP 5,681,543A and Canto *et al.* Claims 34 and 35 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Yoshimoto *et al.* in view of USP 5,681,543A, USP 4,628,027A, and Canto *et al.*, and in further view of USP 6,168,779. Accordingly, the issues surrounding the claims are different, and the claims do not stand or fall together.

ARGUMENT

Issue 1– Whether claims 33 and 36-39 are patentable under 35 U.S.C. § 103(a) as being unpatentable over Yoshimoto et al. (Breast Cancer Res. Treat. 42: 87-90, 1997) in view of U.S. Patent No. 5,681,543 A to Schmitt-Willich, et al., and Canto et al. (Gastrointestinal Endoscopy 44: 1-7, 1996).

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or combined references) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

I. The prior art references of Yoshimoto et al. (Breast Cancer Res. Treat. 42: 87-90, 1997), U.S. Patent No. 5,681,543 A to Schmitt-Willich, et al., and Canto et al. (Gastrointestinal Endoscopy 44: 1-7, 1996) either alone or in combination, do not teach or suggest all the claim limitations of claims 33 and 36-39.

The Examiner has argued that the Applicants cannot show nonobviousness by attacking references individually where the rejections are based upon combinations of references. This is incorrect because, as mentioned above, the Examiner must satisfy all three criteria to establish a prima facie case of obviousness including the criteria that all of the limitations of the claims must be taught or suggested by the prior art. *In re Royka* 490 F.2d 981 (CCPA 1974). If all of the limitations of the claims are not found or suggested in the prior art, there cannot be a *prima facie* case of obviousness regardless of whether or not the rejection was based upon a combination of the references. As the Applicants will show, all of the claim limitations are not taught or suggested in the prior art cited by the Examiner.

A. Yoshimoto *et al.* (Breast Cancer Res. Treat. 42: 87-90, 1997)

The Examiner has maintained the rejection of claims 33 and 36-39 under 35 U.S.C. § 103(a) because "[I]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to identify the location of lesions within a breast duct or breast ductal network for the purpose of conservatively excising the lesion and surrounding tissue by a process according to claims 33 and 36-39 because: (a) Yoshimoto et al. teaches the injection of gadolinium-DPTA into the breast duct to identify the location of such lesions by magnetic resonance imaging for the purposes of excising the lesions and surrounding tissue by conservative surgery..." September 23, 2004 Office Action, page 10, first paragraph. The Applicants respectfully disagree.

Yoshimoto *et al.* does not teach or suggest a method for identifying the location of a lesion within a breast duct or breast ductal network. In fact, Yoshimoto *et al.* teaches away from the claimed invention. Experimental evidence presented in Yoshimoto *et al.* demonstrates that galactography is insufficient at determining the exact location of a breast duct lesion. In the

figure legend of Figure 1(B) of Yoshimoto *et al.* (page 88) it clearly states that "...it is difficult to know the exact location of the disease within the breast from these images." (emphasis added). The Examiner argues that the Applicants have "...manipulatively taken the statement out of context" and further argues that the statement "...clearly addresses the inadequacy of mammography, not of the disclosed methodology." February 2, 2005 Office Action, page 4, next to last paragraph. This is simply not true. Yoshimoto *et al.* does not teach that MR galactography is superior to mammography galactography. In fact, Yoshimoto *et al.* clearly states that MR galactography is "somewhat inferior" to mammography galactography in terms of differential diagnosis (see page 90; second column).

Yoshimoto *et al.* simply does not teach or suggest a method of identifying the specific location of a lesion within a breast duct or breast ductal network. Yoshimoto *et al.* teaches the injection of gadolinium-DPTA into the breast duct of patients with nipple discharge for an evaluation of the extent of the disease. At best, Yoshimoto *et al.* teaches that "[a] combination of both galactography methods may provide more useful information about intraductal lesions in patients with nipple discharge." (see page 90; second column)(emphasis added). One of ordinary skill in the art simply cannot look to Yoshimoto *et al.* to learn a method of detecting the specific location of breast cancer cells within a breast duct or breast ductal network

Thus, Yoshimoto *et al.* does not teach or suggest the present invention because it does not disclose all of the limitations of the pending claims either alone or in combination with any or the other prior art references. Accordingly, the premise on which the rejection is based, i.e. that Yoshimoto *et al.* teaches or suggests a method of identifying the specific location of a lesion within a breast duct or breast ductal network, is not supported by the evidence of record.

B. United States Patent 5,681,543 to Schmitt-Willich, *et al.* (the '543 patent)

The Examiner has maintained the rejection of claims 33 and 36-39 under 35 U.S.C. § 103(a) because "[I]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to identify the location of lesions within a breast duct or breast ductal network for the purpose of conservatively excising the lesion and surrounding tissue by a

process according to claims 33 and 36-39 because "...'543 teaches or suggests that the targeted delivery of gadolinium using a diagnostic compound comprising a gadolinium-containing polymer complex and a targeting agent can be performed advantageously, since a targeted identifying agent targeted to lesions in the breast duct or breast ductal network concentrate in breast duct or breast ductal network and specifically bind lesions of the breast..." September 23, 2004 Office Action, page 10, first paragraph.

The '543 patent teaches polymer-bonded complexing agents and pharmaceutical agents containing them for magnetic resonance imaging. The '543 patent does not teach or suggest the use of such complexing agents to identify the specific location of lesions within breast ducts. In fact, throughout the entire '543 document, there is but a single mention of breast cancer and that is in relation to the use of antibodies specific for a number of tumors including tumors of the gastrointestinal tract, breast, liver, bladder, gonads and of melanoma. Thus the '543 patent does not teach or suggest one of the limitations of the presents claims of using a targeting agent to identify the specific location of a lesion within a breast duct or breast ductal network.

Thus, USP 5,681,543 does not teach or suggest the present invention because it does not disclose all of the limitations of the pending claims either alone or in combination with any or the other prior art references. Accordingly, the premise on which the rejection is based, i.e. that USP 5,681,543 teaches or suggests the administration of an identifying agent targeted to lesions in the breast duct or breast ductal network, is not supported by the evidence of record.

C. Canto *et al.* (Gastrointestinal Endoscopy 44: 1-7, 1996)

The Examiner has maintained the rejection of claims 33 and 36-39 under 35 U.S.C. § 103(a) because "[I]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to identify the location of lesions within a breast duct or breast ductal network for the purpose of conservatively excising the lesion and surrounding tissue by a process according to claims 33 and 36-39 because "...Canto et al. teaches or suggests that washing to remove non-specific bound diagnostic agents can be performed by in vivo endoscopic procedures to improve the specificity of the test by reducing background noise, or the generation

of non-specific, undesired signals." September 23, 2004 Office Action, page 10, first paragraph.

Canto *et al.* simply does not teach or suggest endoscopic procedures for the in vivo washing to remove non-specific bound diagnostic agents to increase the specificity of a diagnostic test. Canto *et al.* teaches the use of methylene blue in an endoscopic procedure to stain specialized columnar epithelium in the esophagus of patients. The Examiner argues that since the reference is entitled: "Methylene blue selectively stains intestinal metaplasia in Barrett's esophagus" the reference therefore teaches or suggests that methylene blue can be used to selectively stain cancer cells. February 2, 2005 Office Action, page 4, last paragraph. A simple reading of text shows that methylene blue does not specifically stain cancer cells and, in particular, there is no teaching or suggestion in Canto *et al.* for the use of methylene blue to stain breast duct lesions. Canto *et al.* states "[p]ositive staining was defined as blue-stained endoscopically normal esophageal mucosa that persisted despite vigorous water irrigation." (see page 2, column 2). Canto *et al.* teaches that methylene blue can be used to stain normal columnar epithelial which is located in the esophageal mucosa. In fact, methylene blue is a well known basic biological dye used extensively as a nuclear stain in cytology, pathology, histology and other fields of plant and animal biology. For example, methylene blue is a well know stain of nuclei of human cheek cells. Methylene blue is also well known as a dye for microorganisms such as bacteria and yeast. Thus, the washing step described in Canto *et al.* can not be used to improve the specificity of the test by reducing the generation of non-specific, undesired signals because methylene blue does not stain specifically. Also, there is nothing in Cato *et al.* that suggests that methylene blue would selectively stain breast cancer cells in a breast duct.

Thus Canto *et al.* does not teach or suggest the present invention because it does not disclose all of the limitations of the pending claims either alone or in combination with any or the other prior art references. Accordingly, the premise on which the rejection is based, i.e. that Canto *et al.* teaches or suggests that washing to remove non-specific bound diagnostic agents can be performed by in vivo endoscopic procedures to improve the specificity of the test by reducing background noise, or the generation of non-specific, undesired signals, is not supported by the evidence of record.

Summary

All of the limitations of the present claims are not taught or suggested in the prior art cited by the Examiner. The present claims teach a method of identifying the location of breast cancer cells within a breast duct or breast ductal network the method comprising providing a compound comprising a targeting agent coupled to an identifying agent; delivering the compound into at least one breast duct and allowing the delivered compound to specifically bind to at least one breast cancer cell within at least one duct or ductal network; washing the breast duct or ductal network with a solution to remove non-specifically bound compound; and detecting the presence of the identifying agent within said breast duct or ductal network. Neither Yoshimoto *et al.*, the '543 patent, nor Canto *et al.* teach or suggest the delivery of a compound into a breast duct which is comprised of a targeting agent coupled to an identifying agent that specifically binds to breast cancer into a breast duct nor do the references teach or suggest the washing of a breast duct or ductal network with a solution to remove non-specifically bound compound, leaving only specifically bound compound, the presence of which identifies the location of breast cancer cells within the a breast duct or breast ductal network.

For these reasons, the rejection of claims 33 and 36-39 under 35 U.S.C. § 103(a), should be reversed.

II. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention. See, *e.g.*, *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

A new combination of elements can be patented "whether it be composed of elements all new, partly new or all old." *Rosmount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546, 221 USPQ 1, 7 (CAFC 1984). The Court of Appeals for the Federal Circuit has forcefully stated that a claim rejection must provide a specific motivation in the art for combining elements from cited art in order to establish obviousness of a new combination.

> "[C]ase law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. ... [Evidence of a suggestion, teaching, or motivation to combine] must be clear and particular. ... Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.' ... [A] reference-by-reference, limitation-by-limitation analysis fails to demonstrate how the [cited] references teach or suggest their combination ... to yield the claimed invention," and a conclusion of obviousness based on such an analysis "as a matter of law, cannot stand." *In re Dembiczak*, 175 F.3d 994, 999, 1000, 50 USPQ2d 1614, 1617, 1618 (Fed. Cir. 1999), emphasis added.

Dembiczak involved patent claims to "a large trash bag made of orange plastic and decorated with lines and facial features, allowing the bag, when filled with trash or leaves, to resemble a Halloween-style pumpkin, or jack-o'-lantern." *Dembiczak*, 996, 1616. The prior art cited by the Board included: a book describing how to teach children to make a "Crepe Paper Jack-O-Lantern;" a book describing a method of making a "paper bag pumpkin" by stuffing a bag with newspapers, painting it orange, and then painting on facial features with black paint; a U.S. Patent describing a bag apparatus wherein the bag closure is accomplished by the use of folds or gussets in the bag material; design patents issued to Dembiczak; and prior art "conventional" plastic lawn or trash bags. The Federal Circuit held that the claimed pumpkin-style trash bag was not obvious because there was no clear, particular motivation to combine the cited references.

This holding of *Dembiczak* that evidence of motivation to combine must be clear and particular to establish obviousness has been emphasized over and over again by the Federal

Circuit since *Dembiczak* was decided. It was strongly reemphasized in *Ruiz v. A.B. Chance Co.*, 57 USPQ2d 1161 (Fed. Cir. 2000):

> In order to prevent a hindsight-based obviousness analysis, we have clearly established that the relevant inquiry for determining the scope and content of the prior art is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references. See, e.g., In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("[T]he Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); In re Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617 ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."). "Determining whether there is a suggestion or motivation to modify a prior art reference is one aspect of determining the scope and content of the prior art, a fact question subsidiary to the ultimate conclusion of obviousness." Sibia Neurosciences, Inc. v. Cadus Pharma. Corp., 225 F.3d 1349, 1356, 55 USPQ2d 1927, 1931 (Fed. Cir. 2000); Tec Air, Inc. v. Denso Mfg., Inc., 192 F.3d 1353, 1359, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999) (stating that the factual underpinnings of obviousness include whether a reference provides a motivation to combine its teachings with those of another reference).
>
> ... there is "a general rule that combination claims can consist of combinations of old elements as well as new elements," Clearstream Wastewater Sys. v. Hydro-Action, Inc., 206 F.3d 1440, 1446, 54 USPQ2d 1185, 1189-90 (Fed. Cir. 2000), "[t]he notion . . . that combination claims can be declared invalid merely upon finding similar elements in separate prior patents would necessarily destroy virtually all patents and cannot be the law under the statute, § 103." Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1575, 1 USPQ2d 1593, 1603 (Fed. Cir. 1987); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997) ("It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements."). *Ruiz* at 1167

Applying this standard to the references cited by the Examiner, it is clear that the Examiner has failed to meet the burden of providing evidence of a motivating force sufficient to compel a person of ordinary skill in the art to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. The motivation cited in the Office Action for the proposed combination is as follows:

> "One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to identify the location of such lesions a breast duct by magnetic resonance imaging for the purposes of excising the lesions and surrounding tissue by conservative surgery."

September 23, 2004 Office Action, page 10, second paragraph. This statement does not provide the clear, particular suggestion in the art for making the specific claimed combination as is required under *In re Dembiczak.* There is no clear, particular suggestion or motivation in the prior art to combine the teachings in the applied references in the proposed manner to arrive at the specific method of identifying the location of breast cancer cells within a breast duct by providing a compound comprising a targeting agent coupled to an identifying agent; delivering the compound into at least one breast duct and allowing the delivered compound to specifically bind to at least one breast cancer cell, washing the breast duct with a solution to remove non-specifically bound compound and detecting the presence of the identifying agent within said breast duct, much less for the claims dependent thereon with their additional limitations.

Yoshimoto *et al.* teaches the injection of gadolinium-DPTA into the breast duct of patients with nipple discharge for an evaluation of the extent of the disease. As mentioned previously, gadolinium-DPTA is a non-specific contrast agent used to identify the entire ductal system, not specific cancer cells. The method of Yoshimoto et al. does not teach or suggest the washing of the breast duct or ductal system to remove the gadolinium-DPTA.

United States Patent 5,681,543 to Schmitt-Willich, et al. (the '543 patent) describes numerous polymer-bonded complexing agents for magnetic resonance imaging. There is no teaching or suggestion in the '543 patent of a compound which is comprised of a targeting agent coupled to an identifying agent which is specific for breast cancer cells in a breast duct.

Throughout the entire '543 patent, there is but a single mention of breast cancer and that is in relation to the use of antibodies specific for a number of tumors including tumors of the gastrointestinal tract, breast, liver, bladder, gonads and of melanoma. The '543 patent also does not teach or suggest the washing of a breast duct or ductal system to remove non-specifically bound polymer-bonded complexing agents. Thus, neither Yoshimoto et al. nor the '543 patent either modified or in combination, teaches or suggests a method for identifying cancerous breast

cells in a breast duct via a compound comprising a targeting agent coupled to an identifying agent; delivering the compound into at least one breast duct and allowing the delivered compound to specifically bind to at least one breast cancer cell within at least one duct or ductal network; washing the breast duct or ductal network with a solution to remove non-specifically bound compound; and detecting the presence of the identifying agent within said breast duct or ductal network.

Canto *et al.* teaches the use of methylene blue to stain specialized columnar epithelium in the esophagus of patients. There is no teaching or suggestion in the Canto *et al.* of a compound which is comprised of a targeting agent coupled to an identifying agent which is specific for breast cancer cells in a breast duct. The Examiner attempts to use Canto *et al* to teach or suggest the step of washing to remove non-specific bound diagnostic agents. As mentioned previously, methylene blue is a non-specific dye used to stain a number different cell types. There is simply no suggestion or motivation to combine Canto *et al* with the teachings of Yoshimoto *et al* and the '543 patent. Canto *et al* teaches a method of using a non-specific dye administered orally to the esophagus of a human to detect specialized columnar epithelium. The differences between the methodologies of Canto *et al* as compared to Yoshimoto *et al* and the '543 patent are too great to believe that an ordinary person skilled in the art would have thought to combine the disparate teachings.

Applicants respectfully submit that the Examiner has, at most, set forth an "obvious to try" rationale in support of this obviousness rejection. However, an "obvious to try" rationale is not the appropriate standard for obviousness under 35 U.S.C. §103 (M.P.E.P. §2145). The Court of Appeals for the Federal Circuit has announced that "[a] general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of the search." In re Deuel, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995). Similarly, in the present case, the general teachings of administering non-specific contrast agents and dyes to patients are not sufficient to make Applicants' invention obvious. *Prima facie* obviousness has not been established under such conditions.

For these reasons, the rejection of claims 33 and 36-39 under 35 U.S.C. § 103(a), should be reversed.

III. There is no reasonable expectation of success.

Under section 103(a), "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in Applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed.Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Applicants believe that the Examiner has failed to establish a *prima facie* case of obviousness, since of Yoshimoto *et al.*, the '543 patent, and Canto *et al.* alone or in combination, fail to provide the necessary expectation of success for the ordinarily skilled artisan to arrive at the claimed invention. The references Yoshimoto *et al.*, '543 patent, and Canto *et al.* all describe the use of non-specific contrast agents or dyes for use in human diagnostics or therapeutics. There would be no expectation that the administration of such non-specific contrast agents and dyes would successfully bind to specific cancer cells in a breast duct or ductal network. Likewise, there would be no expectation that the washing step described in Canto *et al.* would successfully remove non-specifically bound dye in a breast duct because, as mentioned previously, methylene blue is already a non-specific dye so the addition a washing step would not, as the Examiner suggests, increase the specificity of the dye for cancer cells. Lastly, there would be no expectation that the administration of non-specific contrast agents and dyes would successfully identify individual breast ducts or breast ductal networks containing cancerous cells. One of the advantages of the present claims is the ability of the method to distinguish individual ducts in a human breast which contain cancerous cells. By distinguishing individual breast ducts containing cancerous cells from normal breast ducts, the cancerous ducts or the section of the breast duct which contains the cancerous cells may be removed by conservative surgery thus saving the patient from more drastic surgical procedures. There would be no expectation that the administration of non-specific contrast agents and dyes would successfully be able to identify individual ducts from normal ducts due to the non-specific nature of the compounds added.

Thus, the Examiner has failed to establish a *prima facie* case of obviousness, since of Yoshimoto *et al.*, the '543 patent, and Canto *et al.* alone or in combination, fail to provide the necessary expectation of success for the ordinarily skilled artisan to arrive at the claimed invention. For these reasons, the rejection of claims 33 and 36-39 under 35 U.S.C. § 103(a), should be reversed.

Issue 2-- Whether claims 34 and 35 are patentable under 35 U.S.C. § 103(a) as being unpatentable over Yoshimoto et al. (Breast Cancer Res. Treat. 42: 87-90, 1997) in view of U.S. Patent No. 5,681,543 A to Schmitt-Willich, et al., U.S. Patent No. 4,628,027 A to Gay, Canto et al. (Gastrointestinal Endoscopy 44: 1-7, 1996), and U.S. Patent No. 6,168,779 to Barsky, et al.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or combined references) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

I. The prior art references, either alone or in combination, do not teach or suggest all the claim limitations

The Examiner has argued that the Applicants cannot show nonobviousness by attacking references individually where the rejections are based upon combinations of references. This is incorrect because, as mentioned above, the Examiner must satisfy all three criteria to establish a prima facie case of obviousness including the criteria that all of the limitations of the claims must be taught or suggested by the prior art. *In re Royka* 490 F.2d 981 (CCPA 1974). If all of the limitations of the claims are not found in the prior art, there cannot be a prima facie case of obviousness regardless of whether or not the rejection was based upon a combination of the references. As the Applicants will show, all of the claim limitations are not taught or suggested in the prior art cited by the Examiner. The deficiencies of Yoshimoto et al. (*Breast Cancer Res. Treat.* 42: 87-90, 1997), U.S. Patent No. 5,681,543 A to Schmitt-Willich, et al., and Canto et al. (*Gastrointestinal Endoscopy* 44: 1-7, 1996) have been described above.

A. United States Patent 4,628,027 to Gay, *et al.* (the '027 patent)

The '027 patent teaches the use of in vitro diagnostic methods using monoclonal antibodies against connective tissue proteins. The '027 patent specifically teaches the use of monoclonal antibodies to detect changes in collagen profiles in human body tissues and fluids since their concentration ratios are subject to change during certain pathological conditions and during therapeutic regimens for the treatment of such conditions. The '027 patent does not teach or suggest a method of identifying the specific location of a lesion within a breast duct or breast ductal network. The antibodies described in the '027 patent do not specifically recognize cancerous breast cells, but instead recognizes collagen which is a common protein found throughout the human body.

The Examiner provides no argument for the reason why the "027 patent should be considered as a prior art reference against the present claims. Thus the '027 patent does not teach or suggest the present invention because it does not disclose all of the limitations of the pending claims either alone or in combination with any or the other prior art references. Accordingly, the premise on which the rejection is based, i.e. that '027 patent teaches or suggests the use of a complexing agents to identify the location of cancerous breast cells within a breast duct or breast ducts and the coupled compound is delivered to more than one duct on a breast, is not supported by the evidence of record.

B. United States Patent 6,168,779 to Barsky, *et al.* (the '779 patent)

The Examiner has maintained the rejection of claim 34 under 35 U.S.C. § 103(a) because "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to deliver the compound according to claim 34, because "...'779 teaches the disclosed methods comprising cannulation or catheterization of one or all of the individual breast ducts provide a means by which a desired diagnostic material can be instilled through one or more orifices at the surface of the breast and into the lumens of the associated breast ducts." September 23, 2004 Office Action, page 12, second paragraph.

The Examiner has also maintained the rejection of claim 35 under 35 U.S.C. § 103(a) because "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to identify, access, and deliver, to more than one breast duct according to claim 35, because "...'779 teaches methods for identifying each of the orifices at the surface of the breast duct associated with a breast duct and suggests the importance of evaluating the presence of lesions in each individual breast duct, not only the discharging duct, since breast cancer usually arises from a single ductal system and exists in a precancerous state for a number of years." September 23, 2004 Office Action, page 12, third paragraph.

The '779 patent teaches a method for locating an orifice of a breast duct. The '779 patent simply does not teach or suggest a method of identifying the specific location of a cancer cells within a breast duct or breast ductal network. The Examiner states that the '779 patent "...teaches the introduction of suitable diagnostic materials, such as contrast medium, into the breast ducts prior to imaging for the purpose of localizing cancerous lesions of the breast duct epithelium has been previously described by others..." September 23, 2004 Office Action, page 12, first paragraph. It is inappropriate to suggest that the '779 patent teaches a method of introducing contrast medium into breast ducts by pointing to other references. The '779 patent simply does not teach or suggest the use of a complexing agents to identify the location of cancerous breast cells within a breast duct or breast ducts. Also, the '779 patent does not teach or suggest a method of delivering a coupled compound to more than one breast duct or ductal network.

Thus the '779 patent does not teach or suggest the present invention because it does not disclose all of the limitations of the pending claims either alone or in combination with any or the other prior art references. Accordingly, the premise on which the rejection is based, i.e. that '779 patent teaches or suggests the use of a complexing agents to identify the location of cancerous breast cells within a breast duct or breast ducts and the coupled compound is delivered to more than one duct on a breast, is not supported by the evidence of record.

For these reasons, the rejection of claims 34 and 35 under 35 U.S.C. § 103(a), should be reversed.

II. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention. See, *e.g.*, *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applying this standard to the references cited by the Examiner, it is clear that the Examiner has failed to meet the burden of providing evidence of a motivating force sufficient to impel a person of ordinary skill in the art to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. The motivation cited in the Office Action for the proposed combination is as follows:

> "One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to identify the location of lesions in one or more breast ductal networks by magnetic resonance imaging for the purposes of excising the lesions and surrounding tissue by conservative surgery and otherwise clinically intervening in the course of the disease as soon as possible and as deemed appropriate following the localization of any precancerous lesions."

September 23, 2004 Office Action, page 12, last paragraph. This statement does not provide the clear, particular suggestion in the art for making the specific claimed combination as is required. There is no clear, particular suggestion or motivation in the prior art to combine the teachings in the applied references in the proposed manner to arrive at the specific method of identifying the location of breast cancer cells within a breast duct by providing a compound comprising a targeting agent coupled to an identifying agent; delivering the compound into at least one breast

duct and allowing the delivered compound to specifically bind to at least one breast cancer cell, washing the breast duct with a solution to remove non-specifically bound compound and detecting the presence of the identifying agent within said breast duct.

The deficiencies of Yoshimoto et al. (*Breast Cancer Res. Treat.* 42: 87-90, 1997), U.S. Patent No. 5,681,543 A to Schmitt-Willich, et al., and Canto et al. (*Gastrointestinal Endoscopy* 44: 1-7, 1996) have been described above. U.S. Patent No. 4,628,027 A to Gay (the '027 patent) teaches the use of in vitro diagnostic methods using monoclonal antibodies against connective tissue proteins. The '779 patent teaches a method for locating an orifice of a breast duct.

As described above, Canto *et al.* teaches the use of methylene blue to stain specialized columnar epithelium in the esophagus of patients. There is no teaching or suggestion in the Canto *et al.* of a compound which is comprised of a targeting agent coupled to an identifying agent which is specific for breast cancer cells in a breast duct. The Examiner attempts to use Canto *et al* to teach or suggest the step of washing to remove non-specific bound diagnostic agents. As mentioned previously, methylene blue is a non-specific dye used to stain a number different cell types. The Examiner also states that "[f]urthermore, because the '779 teaches aspirated saline washings of the ductal lumen may be collected for further diagnostic use, one ordinarily skilled in the art at the time the invention was made would have been motivated to wash the lumen both to remove non-specifically bound targeting agent before image acquisition and to collect cells for additional diagnostic use." September 23, 2004 Office Action, page 13, first paragraph. Once again, the Examiner is attempting to read teachings into references that simply do not support such an interpretation. The '779 patent does not teach or suggest the step of washing a ductal lumen to remove non-specific bound diagnostic agents. Since none of the references cited by the Examiner teach or suggest a compound that specifically binds cancerous cells in a breast duct, it is impossible that one having ordinary skill in the art would have been motivated to make the claimed invention. One would not have been motivated to wash the lumen both to remove non-specifically bound targeting agent because one having ordinary skill in the art would not have been motivated to add a targeting agent to the breast duct in the first place. The advantage of the present invention over the prior methodology of obtaining breast

cells from ductal lavage is the ability to identify the specific breast duct which may contain cancerous cells. By administering a targeting agent directly into a breast duct and subsequently removing non-specifically bound targeting agent from the duct, a physician may be able to identify not only the presence of precancerous or cancerous lesion, but the exact location within the ductal system of the cells.

There is simply no suggestion or motivation to combine Yoshimoto *et al.* with the '543 patent, the '027 patent, Canto *et al.* and the, '779 patent. The differences between the methodologies of Canto *et al* as compared toYoshimoto *et al.,* the '543 patent, the '027 patent, and the '779 patent are too great to believe that an ordinary person skilled in the art would have thought to combine the disparate teachings.

Applicants respectfully submit that the Examiner has, at most, set forth an "obvious to try" rationale in support of this obviousness rejection. However, an "obvious to try" rationale is not the appropriate standard for obviousness under 35 U.S.C. §103 (M.P.E.P. §2145). The Court of Appeals for the Federal Circuit has announced that "[a] general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of the search." In re Deuel, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995). Similarly, in the present case, the general teachings of administering non-specific contrast agents and dyes to patients and the washings of either non-related tissues or ductal lavage methodologies are not sufficient to make Applicants' invention obvious. It is clear that the combination of select elements from these references is based on hindsight in view of Applicants' disclosure. *Prima facie* obviousness has not been established under such conditions.

Accordingly, the premise on which the rejection is based, i.e. that the '027 patent and the '779 patent, either alone or in combination with the prior art references of Yoshimoto *et al.*, '543 patent, and Canto *et al.*, teaches or suggests a method of identifying the specific location of a lesion within a breast duct or breast ductal network, is not supported by the evidence of record.

For these reasons, the rejection of claims 34 and 35 under 35 U.S.C. § 103(a), should be reversed.

III. There is no reasonable expectation of success.

Under section 103(a), "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in Applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed.Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Applicants believe that the Examiner has failed to establish a *prima facie* case of obviousness since the '027 patent, the '779 patent, Yoshimoto et al., the '543 patent, and Canto *et al.*, alone or in combination, fail to provide the necessary expectation of success for the ordinarily skilled artisan to arrive at the claimed invention.

The references Yoshimoto *et al.*, '543 patent, Canto *et al.*, and the '027 patent, all describe the use of non-specific contrast agents or dyes for use in human diagnostics or therapeutics. There would be no expectation that the administration of such non-specific contrast agents and dyes would successfully bind to specific cancer cells in a breast duct or ductal network. Likewise, there would be no expectation that the washing steps described in Canto *et al.* and the '779 patent would successfully remove non-specifically bound dye in a breast duct.

Lastly, there would be no expectation that the administration of non-specific contrast agents and dyes would successfully identify individual breast ducts or breast ductal networks containing cancerous cells. One of the advantages of the present claims is the ability of the method to distinguish individual ducts in a human breast which contain cancerous cells. By distinguishing individual breast ducts containing cancerous cells from normal breast ducts, the cancerous ducts or the section of the breast duct which contains the cancerous cells may be removed by conservative surgery thus saving the patient from more drastic surgical procedures. There would be no expectation that the administration of non-specific contrast agents and dyes would successfully be able to identify individual ducts from normal ducts due to the non-specific nature of the compounds added.

Thus, the Examiner has failed to establish a *prima facie* case of obviousness, since of Yoshimoto *et al.*, the '543 patent, the '027 patent, the '779 patent, and Canto *et al.* alone or in

combination, fail to provide the necessary expectation of success for the ordinarily skilled artisan to arrive at the claimed invention. For these reasons, the rejection of claims 34 and 35 under 35 U.S.C. § 103(a), should be reversed.

CONCLUSION

In view of the arguments presented above, the Applicants contend that each of claims 33-39 is patentable. Therefore, reversal of the rejections under 35 U.S.C. §103(a) is respectfully solicited.

Respectfully submitted,

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APPEALED CLAIMS

33. A method of identifying the location of breast cancer cells within a breast duct or breast ductal network, said method comprising:

providing a compound comprising a targeting agent coupled to an identifying agent;

delivering said compound into at least one breast duct and allowing said delivered compound to specifically bind to at least one breast cancer cell within at least one duct or ductal network;

washing said breast duct or ductal network with a solution to remove non-specifically bound compound; and

detecting the presence of said identifying agent within said breast duct or ductal network;

wherein the presence of said identifying agent identifies the location of breast cancer cells within said a breast duct or breast ductal network.

34. A method as in claim 33, wherein delivering comprises non-percutaneous cannulation or catheterization of the breast duct.

35. A method as in claim 33, wherein the coupled compound is delivered to more than one duct on a breast.

36. A method as in claim 33, wherein the cells are identified for the purposes of excising tissue surrounding and including the cells.

37. A method as in claim 33, wherein said targeting agent comprises an agent selected from the group consisting of a protein; an antibody; an antibody fragment; a polynucleotide; a small molecule; a liposome; a ligand; a lipid; a peptide; and a receptor.

38. A method as in claim 33, wherein said identifying agent comprises an agent selected from the group consisting of a radioactive agent; a radio-opaque agent; a radiolucent agent; a fluorescent agent; a chemiluminescent agent; and a bioluminescent agent.

39. A method as in claim 33, wherein said detection of said identifying agent is through magnetic resonance imaging or positron emission tomography.